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BIOCOMPOSITE CALCIUM-PHOSPHATE MATERIALS USED IN OSTEOPLASTIC SURGERY

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An osteoconductive biocomposite BAK-1000 is developed, which consists of hydroxyapatite and a silicate matrix similar in its chemical composition to sodium-calcium feldspars. The morphological studies of BAK-1000 biocomposite gave foundations for a conjecture concerning the mechanism of the deposition of collagen, which is the first product of osteogenesis, on the surface of the open pores of the material in a living organism with the formation of strong chemical bonds. Implant sets for maxillofacial surgery and neurosurgery were developed on the basis of BAK-1000 biocomposite and implemented in clinical practice.

The emergence of the new generation of biocomposite implantation materials based on calcium phosphates substantially expanded the possibility of restorative and substitutive osteoplastic surgery, mainly in dentistry, maxillofacial surgery, and neurosurgery. This, in turn, presented new problems related to the manual and machine treatment of these materials in manufacturing implants of needed shapes and sizes, as well as to fitting and fixing implants to the bone bed and exploring the possibilities of medical application of these materials.

The research performed in the field of synthesis of biocomposite materials, determination of their structure, and biological and clinical testing made it possible to establish that the biological activity of materials and their compatibility with an organism are primarily related to the presence in their composition of hydroxyapatite (HA) and tricalcium phosphate (β-TCP). In their chemical composition and crystalline structure, these minerals are similar to the hydroxyapatite contained in bone, which constitutes the mineral matrix of bone tissue. Its content in bones of different structure varies from 40 to 70 wt.%.

The biological activity of calcium phosphate materials depends not only on the phosphate content, but on the material structure as well. Thus, materials with a compact structure are characterized by their surface activity, which ensures the intergrowth of the bone and the implant without encapsulation. Materials with an open porous structure, provided that the pore size ranges within the limits of 100 – 500 μm, exhibit volume activity, in which the emerging bone cells colonize the free space inside the material due to osteoconductivity. Both in the first and in the second case, the application of biocomposite materials provide for the restoration of the biological integrity of the bone and its ability to withstand functional loads. The structures and mineral compositions of some calcium phosphate materials are listed in Table 1 (RF Patent No. 2053737) [1, 2].

The general drawback of the considered biocomposite materials consists in a substantial decrease in the activity of calcium phosphates in a physiological medium, since their synthesis requires a high (above 1200°C) temperature. The exception is the domestic osteoconductive biocomposite BAK-1000, synthesized by sintering nonstoichiometric HA powders and an amorphous silicate matrix at temperatures below 800°C, which makes it possible to preserve the defects of the HA structure in the material and, accordingly, its relatively high resorption capacity.

The main advantages of the currently used implant materials are their mechanical strength, which is comparable to that of bone tissue, and their suitability for the production of

TABLE 1

Material	Structure	Mineral composition, wt.%
Interpore-200 (U.S.)	Crystalline, porous	94 HA, 6 β-TCP
Interpore-500 (U.S.)	The same	94 HA, 6 β-TCP
Ceros-80 (Switzerland)	″	> 98 HA
Osprovit 1.2 (Germany)	″	> 98 HA
Bioapatite (France)	″	> 98 HA
BAK-1000 (Russia)	Amorphous-crystalline, porous	45 HA, 55 amorphous silicate matrix
Calcitite-2040 (U.S.)	Crystalline, compact	> 98 HA
Ostrix NR (U.S.)	The same	85 HA, 15 β-TCP

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TABLE 2

Physicomechanical properties	Spongy bone	Interpore-200	BAK-1000
Weight content of hydroxyapatite, %	up to 40	94	45
Pore size, μm	up to 1000	200	100 – 500
Total porosity, %	65	10 – 90	60
Water absorption, %	65	–	40
Volume weight, kg/m^3	1000	1800 – 200	1000 – 1200
Strength, MPa:			
bending	–	15 – 2	up to 10
compressive	15	25 – 5	20

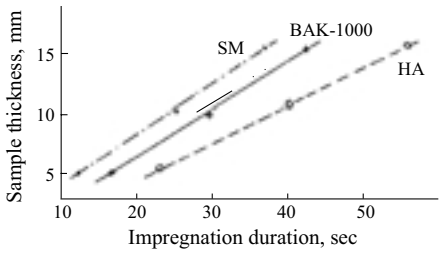

Fig. 1. Duration of impregnation of silicate matrix (SM), biocomposite BAK-1000, and synthetic hydroxyapatite (HA) in 0.01 N NaCl solution depending on sample thickness.

structural implants for spine and skull. At the same time, porous biocomposites (Interpore, BAK-1000, and others) in their physicomechanical parameters are at the same level as spongy bone tissues (Table 2).

Regarding the conditions which are necessary for the process of osteogenesis in the contact zone of the implant and the bone bed, osteoplastic surgeons give clear preference to porous materials which provide for quick infiltration in the medium of the live organism with subsequent osteogenesis inside the implant volume and growth of the emerging bone tissue into the pores, ensuring a firm bond with the bone. As bone cells keep colonizing the pores, the mechanical strength of the implant increases on the average 2 – 3 times [3]. It should be noted as well that porous biocomposite materials are well suited for machine treatment: drilling, milling, cutting, etc., which significantly facilitates their adjustment and fixation to the adjacent bone bed.

One of the most important issues related to the application of structural biocomposite implants is their wettability by the aqueous medium of the body, which depends on their hydrophilicity. The hydrophilic surface of the porous calcium phosphate implant ensures its quick infiltration and diffusive reactions with the body liquids, as a consequence of which the functional groups of organic compounds, primarily, proteins, are adsorbed on the contact surface. In using metallic and, especially, polymeric implants which have hydrophobic surfaces, such processes are retarded. In the case of using hydrophilic calcium phosphate materials, PO_4^{3-} and Ca^{2+} ions actively participate in the exchange processes between the implants and the body medium and facilitate the formation of bone bridges on the implant surface and inside the implant volume.

Study of the process of wetting in biocomposite materials by the aqueous medium was performed using samples of osteoconductive composite BAK-1000 [4] and HA with atomic ratio Ca : P = 1.66.

As opposed to pure calcium phosphate porous ceramics, the BAK-1000 composite is based on a hydrophilic amorphous silicate matrix, which preserves the bioactivity of HA contained in the material in an amount up to 60 wt.%.

In addition to improving the production technology, as BAK-1000 implants are produced by sintering of the matrix powder and HA at relatively low temperatures, the silicate matrix improves the biological properties of the material. Figure 1 shows the duration of impregnation of silicate matrix (SM), BAK-1000 composite, and HA in 0.01 N aqueous solution of HCl, depending on the sample thickness.

In can be seen that for sample thickness up to 15 mm, the impregnation rate is constant. The higher impregnation rate of BAK-1000 composite can be attributed to the fact that it contains a silicate matrix whose surface tension is higher than that of HA. The high hydrophilicity of the multicomponent silicate matrix, which in its composition is close to sodium-calcium feldspars, is the consequence of the fact that it contains active polar OH^- groups formed as the result of leaching.

The bone protein (collagen) as well contains polar groups with positive and negative charges [5]. In addition to the negatively charged OH^- groups contained in the silicate matrix structure, the protein molecules contain such polarized groups as sulfohydril SH^-, carboxyl $-COO^-$, amino H_2N^-, etc. The presence of such a set of polar groups on the contact surface of the BAK-1000 biocomposite and the physiological medium of the organism suggests two possible variants of the precipitation of protein molecules on the open surface of the material. First, the interaction between OH^- groups of the composite and protein can produce reactions of condensation reactions with the formation of strong chemical bonds between the protein and the material, according to the following scheme [6]:

$$-[SiO_3]OH + HO[C_nH_m] \rightarrow$$
$$-[SiO_3] - O - [C_nH_m] + H_2O,$$

or, if HA participates in these reactions:

$$Ca_{10}(PO_4)_6(OH)_2 + HO[C_nH_m] \rightarrow$$
$$Ca_{10}(PO_4)_6(OH) - O - [C_nH_m] + H_2O.$$

Second, as the result of the electrostatic interaction between the oppositely charged polar groups of protein and material components, electrostatic bonds can arise between the protein molecules and the material surface. The strength of these bonds is not high, compared with the valence bonds,

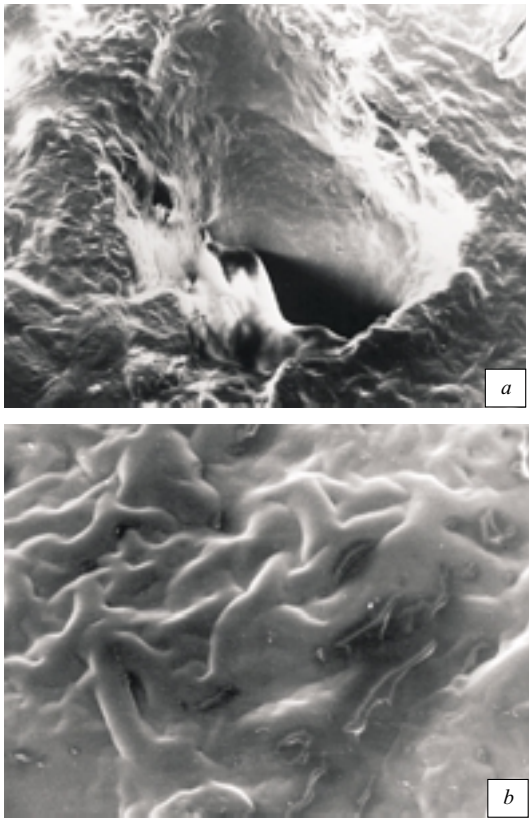

Fig. 2. Electron microscope photos of BAK-1000 samples 7 days after implantation in rabbit bone tissues: *a*) material cell (× 50); *b*) collagen layer on the cell surface (× 500).

but in view of their great number, one can expect rather firm fixation of protein to the material.

Both considered mechanisms of the possible sedimentation of protein molecules are sufficiently probable and can proceed simultaneously.

Figure 2 shows a photomicrograph of open pores of BAK-1000 biocomposite 7 days after engrafting into the bone tissue of a rabbit. It is clearly visible in the photo that all the inner pore surfaces are covered with a collagen fiber layer. Based on the morphological studies conducted throughout a year, it was found that collagen forms the protein matrix of the growing bone tissue. The calcination of collagen fibers with the formation of HA in the form of new bone bridges can be observed as soon as 3 weeks after sample implantation.

The formation and precipitation of crystalline HA bridges on collagen fibers most probably proceeds according to the same mechanism, as collagen precipitation on the hydrated surface of the biocomposite, as the consequence of interaction between polarized groups. As in the case of natural bone tissues, the orientation of HA bridges is determined by the direction of the collagen fibers.

Based on the osteoconductive biocomposite BAK-1000, sets of implants for maxillofacial surgery and neurosurgery have been developed, and over 200 patients with bone injuries, gun wounds, inborn pathology, etc., underwent surger employing these implants. More than five years of clinical studies indicated a sufficiently high effectiveness of the use of biocomposite material BAK-1000 in osteoplastics. The set of implants NIS-R-01 for the correction of cranial defects and deformations is authorized by the Ministry of Health of the RF for application in all specialized clinics of Russia (Fig. 3).

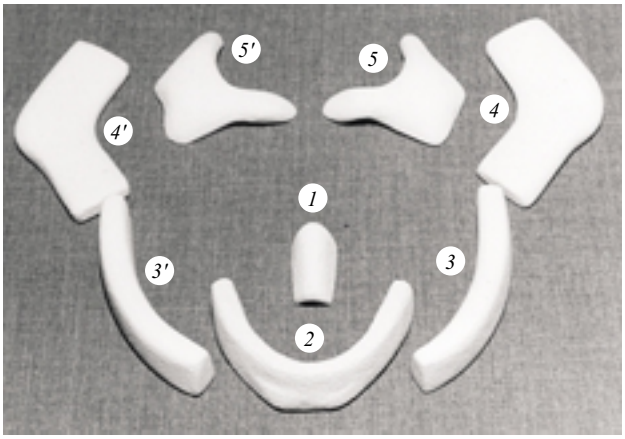

Fig. 3. A set of glass-apatite implants NIS-R-01 for correction of defects and deformations of skull bones: *1*) nose back; *2*) chin sector; *3* and *3′*) lower jaw body (left and right); *4* and *4′*) lower jaw angle (left and right); *5* and *5′*) cheekbone (left and right).

The results of the systematic physicochemical, chemicobiological, and morphological studies of the biocomposite BAK-1000 did not reveal a direct relationship between the resorption capacity of HA made of this material and the osteogenesis process evolving in it. The study of BAK-1000 samples from which HA was completely removed established that no significant morphological distinctions in osteogenesis were observed, except for the fact that young bone bridges emerged about 2 weeks later. It can be concluded that the principal factor in the development of the conditions needed for osteogenesis is the presence of polar groups in the implant material, which induce collagen fiber deposition on this material and therefore ensure subsequent formation and evolution of bone cells.

The development and application of biocomposite materials based on resorbing calcium phosphates is promising in our opinion, subject to the condition that the rate of material resorption in the organism correlates with the rate of bone structure formation, and the osteogenesis process leads to sufficiently full replacement of the implant by the forming bone.

The new modification of osteoconductive composite, i.e., BAK-1000M, satisfies the above conditions. As distinct from the basic material BAK-1000, BAK-1000M is polymineral, since up to 50 wt.% nonstoichiometric HA is replaced by β-TCP, which is more soluble in the physiological medium. The latter modification of the composite served as

the basis for developing a set of structural implants for the restoration and substitution of skull bones.

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